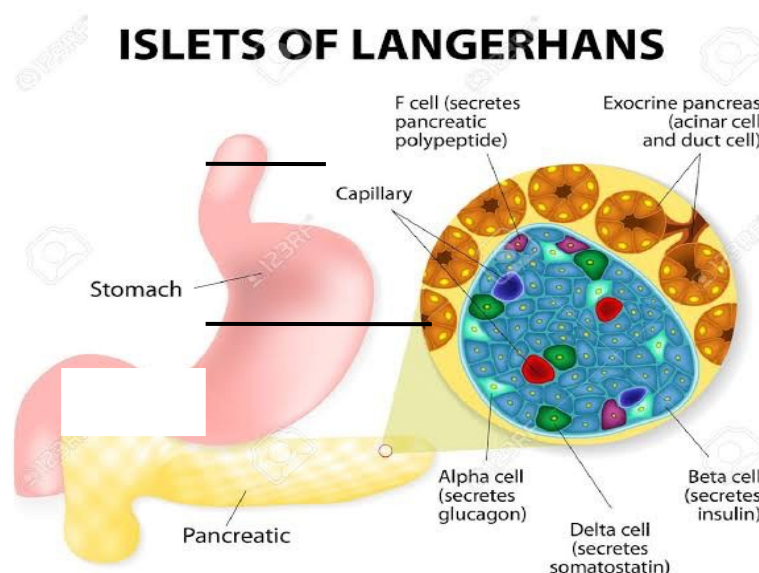


Pancreas (1)

ILOs:**After this lecture, student should be able to:**

- Explain the physiological functions of insulin
- Illustrate how insulin is released from β cells of pancreas in well fed state.
- Describe insulin receptors, the way they mediate insulin action, and the way they are regulated.
- Mention the types & functions of glucose transporters found in the body.
- List the factors that affect insulin secretion.



Physiologic anatomy of an islet of Langerhans in the pancreas

The pancreas is composed of two types of tissues:

1- Exocrine part (Pancreatic acini): Form about 80% of the pancreas and secrete digestive juices into the duodenum.

2- Endocrine part (Islets of Langerhans):

- Human pancreas contains 1 - 2 million islets of pancreas that form about 1% of the pancreas (ducts and blood vessels form the rest).

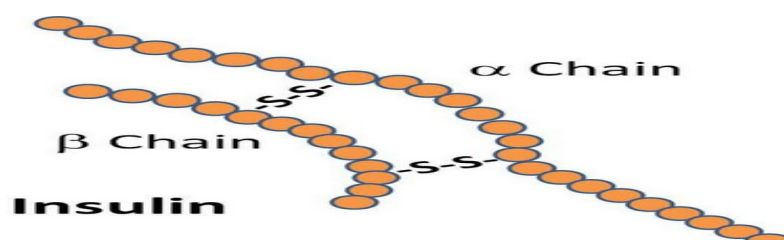
- Each islet has a large blood supply, and blood from the islets drains into the hepatic portal vein.
- There are 4 cell types in the islets which differ in their morphologic and staining characteristics:
 - (α) *A cells*: form 25% of total and secrete **glucagon**.
 - (β) *B cells*: form 60% of all cells and secrete **insulin** and located in the center of each islet.
 - (δ) *D cells*: form 10% of all cells and secrete **somatostatin**.

F cells: form 5% of all cells and secrete **pancreatic polypeptide** (PP) which is concerned with gastrointestinal functions.

- Glucagon, somatostatin, and (PP) are also secreted by cells in GIT mucosa.

Insulin

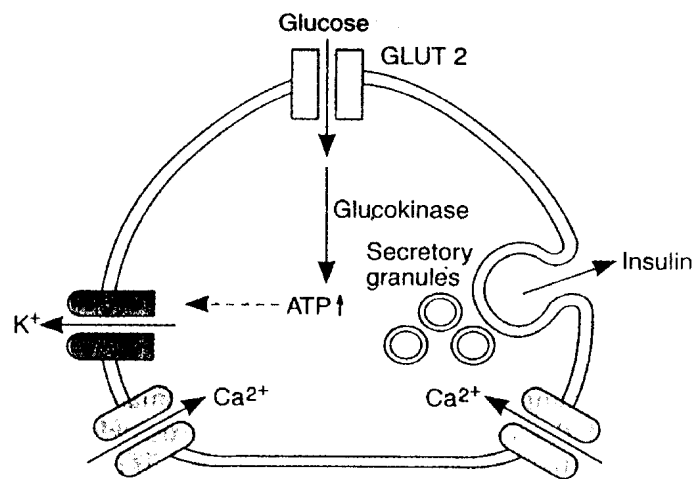
Is a polypeptide containing 2 chains of amino acids (A) and (B) chains linked by disulfide bridges. Minor differences in amino acid composition are present between species.



Mechanism of insulin release:

1. Glucose enters β cells through a special glucose transporter GLUT2.
2. Glucose is oxidized generating **ATP**, which closes **ATP**-sensitive K^+ channels resulting in decreased K^+ efflux and depolarization of β cell membrane.
3. Depolarization opens voltage-sensitive Ca^{++} channels and influxes Ca^{++} inside the β cells. **(Fig.3).**
4. An increase in cytoplasmic Ca^{++} activates Ca^{++} -dependent kinases, that trigger insulin release by exocytosis.

Fig (3): Mechanism of insulin secretion



Mechanism of activation of insulin receptor:

- 1- Insulin receptors are found on many cells in the body, including cells in which insulin does not increase glucose uptake.
- 2- The insulin receptor is a tetramer made up of 4 subunits held together by disulfide linkages: 2 alpha subunits outside the cell membrane, and 2 beta subunits penetrate the cell membrane and protrude into the cell cytoplasm.
- 3- The intracellular portions of the B subunits possess tyrosine kinase activity which is activated after insulin binding to the extracellular alpha subunit.

- 4- Activation of tyrosine kinase of the beta subunits produce autophosphorylation of the beta subunits that phosphorylate some cytoplasmic proteins and dephosphorylate others, via phosphorylation of insulin receptor substrates (IRS-1, IRS-2, IRS-3 and IRS-4)
- 5- The later group activates some intracellular enzymes, and inactivates others

What are the factors modulating insulin receptor?

Modulation of insulin receptor

The number and affinity of insulin receptors are affected by insulin, other hormones and exercise.

- 1- Exposure to increased amounts of insulin decreases the number of receptors (down regulation) as in obesity and acromegaly.
- 2- Exposure to decreased insulin levels increases the number of receptors as in starvation. (up regulation).
- 3- The affinity of the receptors is increased in adrenal insufficiency (decreased glucocorticoids) and in starvation.
- 4- The affinity of the receptors is decreased by excess glucocorticoids.

Cellular effects of insulin stimulation:

Insulin binding to its receptor causes multiple events at several locations, including the cell membrane, the cytoplasm, and the nucleus:

1- Rapid effect (seconds):

- ◆ The membranes of the insulin sensitive cells (muscles, adipose tissue, and liver) become highly permeable to glucose, due to the translocation of the glucose transporters from endosomes to the cell membrane.
- ◆ Insulin also increases the permeability to A.A., K⁺ ions.

2- Intermediate effects (minutes):

Insulin changes the activity of many intracellular metabolic enzymes. These effects result from phosphorylation and dephosphorylation of enzymes.

3- Delayed effect: (hours):

- ◆ Change in the rate of formation of mRNA at the ribosomes & translation to form new proteins.
- ◆ Change in the rate of synthesis of DNA in the nucleus.

Glucose transporters

Group of cell membrane proteins which help transport of glucose across the cell. Glucose transport across the body cells occurs by one of the following mechanisms:

1- Secondary active transport: (Na⁺ - glucose cotransport)

It utilizes sodium - dependent glucose transporters (***SGLT₁*** and ***SGLT₂***) and are responsible for transport of glucose through the **intestine** and **renal tubules**.

2- Facilitated diffusion:

The transporters for facilitated diffusion of glucose are a group of closely related proteins, characterized by:

- a) The different glucose transporters are termed GLUT1 - GLUT7, they vary in their affinity for glucose and each acts in a specific cell.
- b) ***GLUT4*** is the transporter in muscle and adipose tissue that is ***stimulated*** by insulin. ***GLUT4*** molecules are contained in vesicles (endosomes) in the cytoplasm of insulin-sensitive cells. When the insulin receptors of these cells are activated, the vesicles move rapidly to the cell membrane and fuse with it inserting the transporters into the cell membrane. When insulin stimulation stops, patches of cell membrane containing the transporter are

	Function		Major sites of Expression
Secondary active transport (Na⁺- glucose cotransport)			
SGLT1	Absorption of glucose		Small intestine, renal tubules
SGLT2	Absorption of glucose		Renal tubules
Facilitated diffusion			
GLUT 1	Basal glucose uptake		Placenta, blood-brain barrier, brain, red cells, kidneys, colon, many other
GLUT 2	B cell glucose sensor; transport out of intestinal and		B cells of islets, liver. epithelial cells of small intestine, kidneys
GLUT 3	Basal glucose uptake		Brain, placenta, kidneys. many other organs
GLUT 4	Insulin- stimulated glucose uptake		Skeletal and cardiac muscle, adipose tissue,
GLUT 5	Fructose transport		Jejunum, sperm
GLUT 6	None		Pseudogene
GLUT 7	Glucose 6-phosphate transporter in endoplasmic reticulum.		Liver? other tissues

Glucose uptake under the effect of insulin (Insulin stimulated glucose uptake)

a) Insulin stimulates glucose uptake in muscles (skeletal, cardiac, smooth), adipose tissue and liver.

- ◆ In muscle and adipose tissue, insulin facilitates glucose entry by increasing the number of ***GLUT4*** transporters in the cell membranes.
- ◆ Insulin increases the entry of glucose into the liver cells by increasing the activity of glucokinase enzyme that in turn increases the phosphorylation of glucose, so that the intracellular free glucose concentration stays low, facilitating the entry of glucose into the cell through ***Glut2***.

b) Insulin does not stimulate glucose uptake in brain neurons, RBCs, renal tubules, intestinal mucosa, and placenta. In these sites glucose is transported by facilitated diffusion using ***GLUT1, 2, 3& 5; or by secondary active transport using SGLT₁ and SGLT₂***

Metabolic Actions of Insulin

I. On Carbohydrate Metabolism (Hypoglycemic hormone):

Glucose absorbed into the blood stimulates secretion of insulin which in turn causes rapid **uptake**, **storage** and **use** of glucose mainly by muscles, adipose tissue and liver.

A. On muscle :

- 1- Between meals (insulin in blood is small); muscle depends for its energy on fatty acids and not on glucose, because resting muscle membrane is slightly permeable to glucose.
- 2- Following a meal, the rise in blood glucose level stimulates the release of large amounts of insulin.
- 3- Insulin accelerates transport of glucose into muscle fibers by increasing the number of **GLUT4** in their cell membranes.
- 4- Muscles comprise about 50% of body mass, and so muscle uptake of glucose accounts for a major fraction of the lowering of blood glucose level after release of insulin.
- 5- About 20% - 50% of glucose that enters the muscles undergoes oxidation, and the remainder is stored as glycogen, because insulin activates **glycogen synthase**.

B. On Liver:

Glucose is transported freely into liver cells through GLUT2 (insulin – insensitive). The net uptake of glucose into liver cells or its release into blood from the liver depends on whether the concentration of free glucose is higher in plasma or inside hepatic cells.

- 1- **Insulin increases the entry of glucose** from the blood into the liver cells, by increasing the activity of **glucokinase enzyme** which increases G-6-P, so the intracellular free glucose concentration stays low, facilitating the entry of more glucose into the hepatocyte.
- 2- **Insulin promotes glycogenesis:** by increasing the activity of the **enzyme glycogen synthase** in hepatic cells.

3- **Insulin inhibits glycogenolysis:** it inactivates liver **phosphorylase enzyme**, so that breakdown of stored glycogen in liver cells is prevented.

4- **Insulin inhibits gluconeogenesis**

C. On Adipose tissue:

Insulin stimulates the transport of glucose into fat cells by increasing the **number GLUT4 in their cell membranes**.

Most of this glucose is used to form glycerol that combines with fatty acids in adipose cells and facilitates their storage as triglycerides.

II. On Fat Metabolism (Lipogenic & antiketogenic):

Insulin increases the utilization of glucose by most tissues of the body, which decreases the utilization of fat, thus, insulin acts as "**fat sparer**".

1- Insulin promotes FA synthesis in liver.

Insulin promotes conversion of the excess glucose into **FFAs** which are packaged as **triglycerides** in VLDL and transported by blood to adipose tissue.

2- Insulin promotes storage of circulating fat in adipose tissue: (lipogenesis):

a) Insulin activates the enzyme **lipoprotein lipase** in adipose tissue, which splits triglycerides into FFAs, and helps their transfer into adipose cells.

b) FFAs combine with **glycerol** inside the adipose tissue to be stored in the form of triglycerides.

3- Insulin inhibits release of stored fat from adipose tissue into blood: Inhibits lipolysis:

- a. Insulin inhibits the **hormone-sensitive lipase** enzyme in adipose tissue. So the release of FAs from adipose tissue into blood is inhibited.
- b. Insulin stimulates the use of ketoacids by peripheral tissues, thus, **insulin is the major antiketogenic hormone.**

III- Effect of Insulin on Protein Metabolism and Growth (Anabolic):

A- On Protein Metabolism:

Insulin is a general anabolic hormone.

- 1- It increases transport of A.A. into cells and so lowers their plasma level.
- 2- Insulin inhibits protein catabolism (proteolysis) in muscle as it suppresses the release of A.A. from muscle and inhibits their oxidation.
- 3- Inhibits the rate of gluconeogenesis inside the liver, so amino acids are conserved in the form of proteins inside the body cells.

B- On Growth:

Growth is an anabolic state mainly in cartilage, bone and muscle, Insulin stimulates transcription of gene of IGF-I. Thus, more IGF-I is left free in plasma. Thus insulin indirectly affects growth.

Factors regulating insulin secretion

I- Feedback effect of blood glucose level:

- a- Glucose is the most important stimulant for insulin release in humans. At the normal fasting blood glucose level (80 – 100 mg %), the rate of insulin secretion is minimal (basal). If blood

glucose level is suddenly increased, insulin secretion increases markedly, and reaches its maximum at a blood glucose level of 300 mg%.

b- Insulin secretion occurs in two stages, **rapid phase** starts within 3 to 5 minutes from elevation of blood glucose & lasts 15 min (preformed insulin) and **delayed phase** from 15 min to 2 hours (preformed and newly formed insulin).

c- The response of insulin secretion to a rise in the blood glucose level provides an extremely important feedback mechanism for regulating blood glucose level: Rise in blood glucose, increases insulin secretion which leads to increased transport of glucose into muscle, adipose tissue and liver and so blood glucose is lowered to normal level.

2- Amino Acids:

a- Insulin secretion is also stimulated by some A.A. (e.g. arginine and lysine) that result from digestion of protein in a meal.

3-Gastrointestinal Hormones:

Oral glucose leads to an increase in insulin secretion more than when glucose is administered i.v, this is due to:

a- The release of **incretin hormones** (glucagon-like polypeptide- I **GLP-I** and glucose-dependent insulinotropic polypeptide = gastric inhibitory peptide **GIP**), gastrin, secretin and CCK (**insulinogogues**).

4- Other Hormones:

- Glucagon stimulates insulin release.

- Somatostatin inhibits insulin secretion.
- **Cortisol, growth hormone** and **thyroid hormones**; act by directly or indirectly cause hyperplasia of β cells that leads to an increase in insulin secretion.

Also, they antagonize the insulin action on peripheral tissues.

Prolonged secretion in any one of them in large quantities can lead to exhaustion of β cells and cause diabetes mellitus.

5- cAMP: β -adrenergic stimulants, glucagon, theophylline and GIP, increase cAMP levels in β -cells, which in its turn increase insulin secretion through increasing intracellular Ca^{++} .

6- Autonomic Nerves:

- a. Stimulation of vagus nerve increases insulin secretion via action of acetylcholine on M4 receptors.
- b.** Stimulation of the sympathetic nerves to the pancreas inhibits insulin secretion by acting on α_2 -adrenergic receptors.

Relation of insulin to potassium

1- Insulin causes K^+ to enter cells, due to the increased activity of $Na^+ - K^+$ ATPase in cell membranes. Clinically Infusion of insulin and glucose lowers plasma K^+ level and is used effectively for a temporary relief of hyperkalemia in patients with renal failure.

2- K^+ depletion decreases insulin secretion, K^+ - depleted patients (patients with primary hyperaldosteronism) develop glucose tolerance that are restored to normal by K^+ repletion.